Docket No.: **1259-001**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	)	
	)	
Bojidar Stankov	)	Group Art Unit: 1616
	)	
	)	Examiner: Choi, Frank I.
	)	
Serial No.: 09/854,802	)	
	)	
Filed: May 14, 2001	)	

For: CONTROLLED RELEASE FORMULATION CONTAINING AND ACTIVE INGREDIENT, PREFERABLY MELATONIN AND THE METHOD OF PREPARATION

New York, NY 10036
October 14, 2003

MS AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

LETTER

Sir:

Attached are three copies of an Appeal Brief in compliance with 37 CFR§1.192.

Also attached is a check for $165.00 in payment of the Appeal Fee.

Respectfully submitted,

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Docket No.: 1259-001

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Bojidar M. Stankov	)	Group Art: 1616
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For: CONTROLLED RELEASE FORMULATIONS CONTAINING AN ACTIVE INGREDIENT, PREFERABLY MELATONIN AND THE METHOD OF PREPARATION

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MS Appeal
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APPEAL BRIEF

This is an appeal from the final rejection of claim 12.

(1) Real party in interest. The real party in interest is Ambros Pharma S.r.l.

(2) Related appeals and interferences. There are no related appeals or interferences.

(3) Status of the claims. Claims 16-24 are in the application and all of these claims have been finally rejected.

(4) Status of amendments. There are no unentered amendments.

(5) Summary of invention. The present invention provides new formulations for the controlled release of melatonin that are able to "mimic" the physiological pattern of melatonin in the peripheral blood. The new formulations are designed to initially release melatonin quickly at first and thereafter slowly and gradually. The invention provides controlled

release formulations as, medicines and nutritional or health food supplements for the treatment of sleep disturbances.

(6) Issues.

Are Claims 16, 18, 19, 21 and 22 anticipated under 35 U.S.C.§102(b) or in the alternative obvious under 35 U.S.C.§103(a) by Lee et al. (1999) or Lee et al. (1997)?

Are claims 16-24 unpatentable over Lee et al. (1999) or Lee et al. (1997) in view of Bromet or Flaugh under 35 U.S.C.§103(a)?

(7) Grouping of claims. Claims 16, 17, 19, 21 and 22-24 are to be considered together and claims 18 and 20 are to be considered together.

(8) Argument.

Claims 16, 18, 19 21 and 22 have bee finally rejected as being anticipated by or in the alternative under 35 U.S.C.§103(a) as obvious over Lee et al (1999) or Lee et al. (1997).

Claim 16 points out controlled release formulations of melatonin for use as nutritional or health food supplements as noted at page 1, lines 26-29 of the specification. Claims 17 and 20 recite particular amounts of melatonin that are disclosed at page 4, lines 15-16. Claim 18 recites the preferred components as set forth in Example 1. Claim 19 specifies preferred in vitro release rates according to the method disclosed at page 9, lines 25-29 with the release values as disclosed at page 12, lines 1-5. Claim 21 points out a range of initial maximum plasma levels that are provided by the formulation of the invention as disclosed at page 6, lines 6-8. Claim 22 points out preferred in vivo release rates as disclosed at page 4, lines 1-7. Claims 23 and 24 point out the method of inducing and maintaining sleep in one suffering from a sleep disorder by the use of preferred formulations of the

invention.

The rejection over Lee et al. (1999) or Lee et al. (1997) is in error because the cited reference fail to disclose the claimed invention.

Lee et al. (1999) disclose a controlled release tablet of melatonin that is made with a synthetic methacrylic/acrylic Eudragit controlled release membrane polymer which is not approved for use in nutritional food supplements. Since the term "nutritional food supplement tablet" as used in claim 16 precludes the use of a Eudragit type membrane coating, Lee et al (1999) cannot anticipate the tablet as defined by new claim 16. Claim 17 points out a tablet where the nucleus has from 1-3 mg of melatonin. Lee et al, (1999) describe a tablet weighing 52.7 +/-2.0mg which contains 1.6% of melatonin (page 73). This is equivalent to about 0.8mg of melatonin in the core of the Lee et al. (1999) tablet which does not anticipate or suggest a range of 1-3mg of melatonin as pointed out in claim 17.

The concept behind the Lee et al. (1999) tablet is to provide a controlled release coating on the outer layer that provided a biphasic, zero order releasing tablet. Lee et al. (1999) do not disclose or suggest the elimination of the outer release membrane coupled with the addition of an immediate release coating or cortex as pointed out in all of the newly presented claims. The zero order data of Lee et al. (1999) (page 74) shown by Lee etal. (1999) is consistent with the Lee et al. (1999) teachings that the release of the melatonin takes place at a low initial rate and that rate per unit of time is essentially constant when each phase of release is considered. The result is a melatonin dosage form that does not provide an immediate loading dose which results in a plasma profile as shown in Fig. 1. The concept of an immediate loading does is pointed out in the claims by the language of part (b) which specifies that the claimed dosage form must have a "fast release cortex coating" and part (a) which must have a slow release nucleus. The claim terms "fast" and "slow" point out the invention in such a manner as to distinguish the

claimed subject matter from the dosage form of Lee et al. (1999) because these types of release properties are responsible for the plasma profile of Fig. 1 which is distinctly different from the plasma profile of the dosage form taught by Lee et al. (1999). The fast release provides a benefit in that sleep induction is more rapid and nothing in Lee et al. (1999) suggests the making of a completely different dosage form of melatonin. Claim 22 points out the time for the fast release of melatonin from the cortex of the Applicant's dosage form.

The Examiner has urged that the Applicant has not shown that the prior art composition is not capable of acting as the claimed invention. The Applicant has pointed out that the cited reference shows that the prior art composition has a biphasic zero order release profile which means that there is no fast releasing portion. This is evident from Fig. 3 on page 75 of Lee et al. (1999) which shows that there is no immediate release peak that is provided by the Lee et al. (1999) dosage form. For these reasons, Lee et al. (1999) cannot anticipate of make obvious the claimed subject matter.

Claim 21 points out in vivo plasma levels which cannot be achieved using the Lee et al. (1999) teachings. Claims 23-24 point out the method of inducing sleep using certain formulations of the invention. Test data regarding the efficiency of the two-peak formulations of the invention are set forth on page 15, line 8-15.

The Lee et al. (1997) Abstract does not add any disclosure to the Lee et al. (1999) publication. This publication does mention delivery of melatonin within "circadian rhythmic variations" which appears to be a teaching of gradually increasing release rates of a biphasic zero order release dosage form. There is no suggestion which would direct any worker in the art to make a melatonin tablet that provides a plasma profile as described in Fig. 1 of the present application.

The Bromet and Flaugh patents were applied in combination with the Lee et al. (1999) and Lee et al. (1999) references to

reject all of the claims under 35 U.S.C.§103(a).

The Bromet patent is concerned with a two layer mucoadhesive tablet that has a "loading dose layer" and a "programmed release layer". The specification at col. 4, line 7 refers to a tablet layer as a "rapid-release" layer which is defined as "an immediate flash release which may be sustained for 2 to 5 hours". A Carbopol resin is always added to the "slow release" layer of Bromet and it is understood that this product is not approved for use in foods as is hydroxypropylmethyl cellulose which is the specific agent of the Applicant's claims.

In this regard, claims 18 and 20 exclude the possibility of the presence of any Carbopol as the dosage form is limited to hydroxypropylmethyl cellulose and melatonin by the term "consisting essentially of". Nothing in the cited prior art discloses or suggests a melatonin tablet having the claimed ingredients and release characteristics.

The in vivo blood profile of the Bromet formulation (col. 8, lines 15-25) shows that the highest concentration of melatonin is achieved at about 2 hours with a second peak at 6 hours. The data in Fig. 1 of the present application shows that the first peak is obtained at less than one hour which distinguishes the Bromet "rapid release" component from the applicant's "fast" component. The second peak provided by the applicant's tablet is between 2 and 3 hours while the Bromet second peak is at about 6 hours. The Bromet teachings, when considered alone or in combination, fail to suggest the applicant's fast release concept using hydroxypropylmethyl cellulose and a slow release core.

The Federal Circuit has said that when prior art references require selective combination in order to render an invention obvious, there must be some reason for the combination other than hindsight gleaned from the invention itself. Interconnect Planning Corp. v. Feil, 227 U.S.P.Q. 543, 551 (Fed. Cir. 1985). In the present case, there is no teaching in the prior art as to how to make a nutritional food supplement based on melatonin. The materials used to make

different types of controlled release melatonin products of the prior art do not suggest how to make a food supplement product which does not utilize the acrylic and Carbopol materials of the cited prior art.

The Flaugh patent is only concerned with synthetic melatonin derivatives and it fails to suggest any two component controlled release formulation. For these reasons, this patent does not render the claimed invention unpatentable.

For these reason, it is requested that the rejections of record be reversed and patent protection allowed to an advance in the art.

Respectfully submitted,

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(9) Appendix.

16. A controlled release nutritional food supplement tablet which comprises:
(a) a slow release nucleus comprising melatonin and hydroxypropylmethylcellulose;
(b) a fast release cortex coating on said nucleus which comprises melatonin and hydroxypropylmethylcellulose.

17. The nutritional food supplement tablet as defined in claim 16 which comprises:
(a) a slow release nucleus comprising from 1 to 3 mg of melatonin and hydroxypropylmethylcellulose;
(b) a fast release cortex coating on said nucleus which comprises 0.5-1.5mg of melatonin and hydroxypropylmethylcellulose.

18. The nutritional food supplement tablet as defined in claim 16 which consists essentially of:
(a) a slow release nucleus consisting essentially of melatonin and hydroxypropylmethylcellulose;
(b) a fast release cortex coating on said nucleus which consist essentially of melatonin and hydroxypropyl methylcellulose.

19. The nutritional food supplement tablet as defined in claim 16 which comprises:
(a) a slow release nucleus comprises melatonin and hydroxypropylmethylcellulose wherein 95% of the melatonin is released within 5 hours in an oscillating tray containing intestinal juice;
(b) a fast release cortex coating on said nucleus which comprises melatonin and hydroxypropyl methylcellulose wherein 95% of the melatonin is released within 10 minutes in an oscillating tray containing gastric juice.

20. The nutritional food supplement tablet as defined in

claim 16 which consists essentially of:
(a) a slow release nucleus consisting essentially of 1-3 mg of melatonin with hydroxypropylmethylcellulose;
(b) a fast release cortex coating on said nucleus which consists essentially of 0.5-1.5 mg of melatonin with hydroxypropyl methylcellulose.

21. The nutritional food supplement tablet as defined in claim 16 which comprises:
(a) a slow release nucleus comprising melatonin and hydroxypropylmethylcellulose;
(b) a fast release cortex coating on said nucleus comprising melatonin and hydroxypropyl methylcellulose wherein said tablet provides a maximum plasma level of 1,000 to 2,000 pg/ml of melatonin upon in vivo administration.

22. A controlled release nutritional food supplement tablet which comprises:
(a) a slow release nucleus comprising melatonin and hydroxypropylmethylcellulose which releases the melatonin over a 5 to 7 hour period in vivo;
(b) a fast release cortex coating on said nucleus comprising melatonin which releases the melatonin in 5-10 minutes in vivo.

23. A method of inducing and maintaining sleep which comprises the administration of the formulation of claim 16 to one who suffers from a sleep disorder.

24. A method of inducing and maintaining sleep which comprises the administration of the formulation of claim 20 to one who suffers from a sleep disorder.